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THE PATENTS ACT, 1970.

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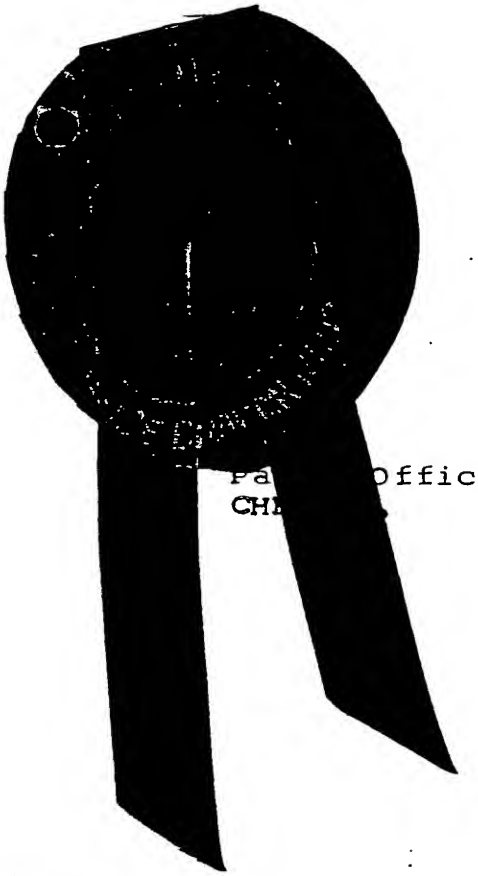
IN00/79

It is hereby certified that annexed hereto is a True Copy of the Provisional and Complete Specifications filed in respect of Patent Application No. 968/MAS/99 dated 1st October, 1999 by Natco Pharma Limited, an Indian Company, having itsregistered Office at Natco House, Road No. 2, Banjara Hills, Hyderabad - 33, India.

In witness thereof
I have hereunto set my hand

Dated this the 09th day of October, 2000.
17th day of Asvina, 1922 (SAKA).



(S. Chandrasekaran)
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FORM 2

THE PATENTS ACT, 1970

PROVISIONAL SPECIFICATION

(Section 10)

A SOFT GEL CAPSULE FOR ORAL ADMINISTRATION OF BENZIMIDAZOLE DERIVATIVES.

Natco Pharma Limited an Indian Company registered under the Indian Companies Act 1956, having its registered office at NATCO House, Road No.2, Banjara Hills, Hyderabad – 33, India.

This specification describes the nature of the invention.

The present invention relates to a soft gel capsule composition resistant to digestive juice made up of gelatin and an enteric polymer in the form of free acid or salt of the same and a method for preparing such soft gel capsule. The soft gel capsule is suitable for incorporating a pharmaceutical composition containing a benzimidazole derivative used in the treatment of duodenal ulcers. These capsules are optionally treated with a gelatin cross linking agent to further harden the capsule shell and/ or an acid to partially convert the polymer salt to free acid or to neutralise the excess alkali used to dissolve the polymer.

Benzimidazole derivatives such as Omeprazole, Lansoprazole Timoprazole and Pantoprazole etc., are known potent proton pump inhibitors with powerful inhibitory action against the secretion of gastric juice (Lancet, Nov. 27, 1982 pages 1223-1224). They are used in the treatment of Zollinzer – Elision syndrome and stress related oesophagitis ulceration. The derivatives are well known and are described, for example in EP-A 0005129.

It has been found that these benzimidazole derivatives, and in particular omeprazole, are susceptible to degradation in acid and neutral media and it is known to protect oral dosage forms by providing an enteric coating. In this way, the active material is protected from acidic gastric juices until it reaches the desired site of release, e.g. the small intestine. Because certain enteric coatings can themselves be, or contain, acidic material, it is also often required to protect the benzimidazole derivatives from the acidity of the enteric coating. For example, it is known to formulate the benzimidazole derivatives with an alkaline material before applying the enteric coating, it is also known to provide an intermediate coating between the benzimidazole derivative and the enteric coating. Generally the intermediate coating is selected so as to be substantially water-soluble or water-dispersible.

EP-A-024 7983; US 4,786,505; US 4,853,230 and US 5,385,739 describe oral pharmaceutical preparations of benzimidazole derivatives that are potent inhibitors of gastric acid secretion, which are composed of a core material in the form of small beads or tablets containing one of the benzimidazole derivatives, particularly omeprazole, together with an alkaline reacting compound, the core material having one or more inert reacting sub-coating layers thereon and providing a final outer enteric coating. Although the above-described compositions are reasonably stable over an extended period of storage, discoloration of the pellets and / or tablets with reduced gastric resistance and reduction of dissolution rate in alkaline buffers was observed.

In a German patent DE 32 22 476 there is a description of a soft gelatin capsule that is resistant to digestive juice, whose wall consists of a usual gelatin mass and which contain polyvinyl acetate phthalate, hydroxypropyl methyl cellulose phthalate or a vinyl acetate / crotonic acid copolymer and/or an alkali metal salt, ammonia salt or amino salt of the same in their wall , and yield their contents readily in the intestines within the prescribed time. The capsules are further treated on the surface with an aldehyde-coating agent.

The present invention takes as basis the production of soft gelatin capsules in the conventional manner using gelatin mass in the known composition and to additionally incorporate substances into the gelatin shell which are insoluble up to a pH value of 6 in aqueous media, but quickly dissolve above this pH value. The capsule shell composition described in DE 32 22 476 above, if used as such for manufacturing capsules containing one of the benzimidazole derivatives in a conventional manner, the free acidic groups of the polymer in the composition reacts with the benzimidazole derivatives and reduces the efficacy of the product during its storage / shelf life period. This problem has been overcome by the invention disclosed.

Accordingly, the main objective of the present invention relates to the intestine dissoluble soft gel capsules composition consisting of gelatin and an enteric polymer in the form of a free acid or its salt characterised by the fact that the pharmaceutical composition consisting of benzimidazole derivatives, in particular omeprazole, incorporated in an oily base is stable during shelf storage and offers protection for more than 2 hrs in artificial gastric juice. Thus according to the preferred objective present invention there is provided a soft gel capsule composition resistant to gastric acid and readily soluble in intestinal juice, comprising of gelatin and an enteric polymer in the form of the free acid or as its salt. The outer surface of the capsule may optionally be treated with a gelatin cross-linking agent to harden the outer surface of the shell and/or an acid solution under cold conditions to partially convert the polymer salt to free acid which offer better gastric resistance.

Still another objective of the invention is to provide a pharmaceutical composition for carrying the benzimidazole derivatives, to be filled into the soft gel capsules, that reduces degradation of the benzimidazole derivatives during storage / shelf life by reacting with free acid groups on the inner surface of shell wall and acts as a buffering agent neutralising the hydrogen ions those permeate into the capsule during *in vitro* testing for gastric resistance and dispersing the contents in aqueous media, once the outer capsule shell is dissolved, during *in vitro* testing in alkaline buffer. The carrier

base is composed of a hydrophobic oily substance, an alkaline inert reacting material as a buffer and a surface active agent which acts as a solubilising and / or dispersing agent.

According to another feature of the invention there is provided a process for preparation of soft gel capsules for containing benzimidazole derivatives that are resistant to the digestive / gastric juice comprising of a usual gelatin mass and an enteric polymer in the form of a free acid or as its salt.

In a preferred embodiment of the invention, the enteric polymer used in the soft gel capsule composition may be selected from among the polmers but not limited to free acid forms of cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, methacrylic acid ester copolymers and the like or their ammonia or alkali metal salts. The amount of such enteric polymer employed may range from 10.0 – 60.0 percent, preferably 20.0 – 40.0 % percent by weight with reference to the dried shell.

The gelatin mass is made up of a composition and method known in the art contains gelatin, a plasticizer, preservatives, colourants, opacifiers, flavours etc., as required.

In order to carryout faster dissolution of the enteric polymer for preparing the capsule composition, the polymer is first dispersed in water, then aqueous solution of ammonia or alkali metal salt is mixed while stirring. When alkali metal salt is used it may be selected from substances such as sodium hydroxide, potassium hydroxide, carbonate of hydrogen sodium, carbonate of hydrogen potassium, sodium carbonate, potassium carbonate etc. The quantity of the base materials used shall be sufficient to neutralise 60 to 100 percent of the free acid groups present in the selected enteric polymer.

The excess ammonia or alkali has to be removed from the capsule shell composition to avoid decomposition of the ester couplings in enteric polymers. When aqueous ammonia solution is used to prepare polymer solution, the excess ammonia shall be removed before capsule manufacturing, after mixing with the gelatin mass, by mixing the mass under reduced pressure in warm condition.

When alkali metal salts are used, the excess alkali shall be neutralized by treating the capsules with an acid selected from any of the following ones, hydrochloric acid, sulfuric acid, nitric acid, in organic acids such as phosphoric acid, mono carbonic acids such as acidic acid, propionic acid,

benzoic acid etc., multi valent carbonic acids such as oxalic acid, propionic acid, maleic acid, fumaric acid etc. The acids are used in the form of cold aqueous solutions in the concentration range of 3 to 30% depending on the type of acid used. The acid treatment shall be carried out after manufacturing and partial drying of the capsules to avoid deformation and / or leakage of the capsule contents.

According to another feature of the invention the soft gel capsules are optionally treated with a cross-linking agent that reacts with gelatin and makes it insoluble in gastric juice. The cross-linking agent may be selected from among the aldehydes such as formaldehyde, glutaraldehyde, 1,2-phthalic acid aldehyde, 1,3-phthalic acid aldehyde, 1,4-phthale acid aldehyde or carbodiimides like 1-ethyl-3-[2-morpholinyl-(4)-ethyl]-carbodiimide-metho-p-toluene-sulfonate. The treatment is done by either coating 0.5 to 1.0% w/v of the substance in an alcohol containing aqueous solution or mixing these substences in the gelatin mass before capsule manufacturing.

According to another feature of the invention the pharmaceutical composition containing benzimidazole derivative, known for its potent proton pump inhibition with powerful inhibitory action against the secretion of gastric juice, is prepared by suspending and/or solubilising the benzimidazole derivative in a carrier mixture composed of a hydrophobic carrier material, an alkaline material and a surface active agent. The amount of such benzimidazole derivative may range from 10.0 to 60.0mg per capsule depending on the benzimidazole derivative used.

The hydrophobic oily material may be selected from among the following: fats and oils (vegetable oils such as sesame oil, corn / maize oil, soybean oil, animal oils such as fish oil, beef oil, pig oil etc.), esters of straight chained aliphatic oils contained in glycerol such as Sunsoft 700 P-2 (a monoester substance manufactured by Taiho Chemicals Company) Panasete 810 (a triester substance, manufactured by Nippon Oils and Fats) or hydrogenated vegetable oils or a mixture thereof. The amount of such hydrophobic oily material may range from 50.0 to 80.0 percent of the pharmaceutical composition.

The alkaline buffering material present in the pharmaceutical composition may be selected from among but are not restricted to substances such as the sodium, potassium, calcium magnesium and aluminum salts of phosphoric acid, carbonic acid, citric acid, other suitable organic or inorganic acids;

substances used in antia[redacted]preparations; meglumine; triet[redacted]olamine etc. The amount of such alkaline buffering material present in the composition may range from 5.0 to 40.0 percent, preferably 10.0 to 25.0 percent by weight of the pharmaceutical composition.

The surface active agent used as solubilising and / or dispersing agents is selected from among but are not restricted to substances such as glyceryl monostearate, polyoxyethylene castor oil derivatives such as Cremophor RH 40 (Make : BASF Corporation), polyoxy ethylene sorbitan fatty acid esters, sodium lauryl sulphate, docusate sodium etc. The amount of such surface active agent present in the composition may range from 2.0 to 20.0 percent preferably 5.0 to 15.0 percent by weight of the carrier composition.

The seamless soft gel capsules are manufactured on a rotary die machine filling with the liquid and / or semi solid pharmaceutical composition containing benzimidazole derivatives.

Advantages of the invention:

The advantages of the present invention are

1) Provide sample Pharmaceutical composition for preparation of a stable formulation of benzimidazole derivatives.
2) Simple method of manufacturing, when compared to the methods disclosed in the prior art.
3) improved bioavailability when compared to the enteric coated pellets as the medicament is solubilized or suspended in the pharmaceutical composition filled into the soft gel capsule.

Dated this 1st day of October, 1999

(P.KHADGAPATHI)
Natco Pharma Limited

ABSTRACT

The present invention relates to a soft gel capsule composition which is resistant to gastric juice and dissoluble in intestine and is suitable for incorporating pharmaceutical composition containing a benzimidazole derivative which require protection from acidic gastric juice until it reaches the small intestine, comprises of a usual gelatin mass and an enteric polymer in the form of the free acid or its salt, surface of the capsule may optionally be treated with a gelatin cross linking agent and / or an acid solution to convert the polymer salt to free acid and a method for preparing such soft gel.

The pharmaceutical composition carrying a benzimidazole derivative either in suspension or solution comprises of hydrophobic oily substance, an alkaline inert reacting substance and a surface active agent.

To,
The Controller of Patents,
The Patent Office Branch,
Chennai.

FORM 2

THE PATENTS ACT, 1970

COMPLETE SPECIFICATION

(Section 10)

968/MAS/99
1-10-99

AN IMPROVED PHARMACEUTICAL COMPOSITION AND A PROCESS FOR ITS PREPARATION.

Complete after provisional
Left 26 APR 2000

ORIGINAL

Natco Pharma Limited an Indian Company registered under the Indian Companies Act 1956, having its registered office at NATCO House, Road No.2, Banjara Hills, Hyderabad – 33, India.

This specification describes the nature of the invention and the manner in which it is to be performed.

The present invention relates to an improved pharmaceutical composition. The present invention particularly relates to an improved pharmaceutical composition, in the form of a soft gel capsule resistant to digestive juice. The composition of the present invention is made up of gelatin and an enteric polymer in the form of free acid or its salt, containing a benzimidazole derivative used in the treatment of duodenal ulcers, solubilised and/or suspended in a liquid or semisolid medium, comprising of a hydrophobic carrier, an alkaline inert reacting material and a surface active agent and/or a solubilising agent. The present invention also relation to a method for preparing the above said pharmaceutical composition.

Benzimidazole derivatives such as Omeprazole, Lansoprazole Timoprazole and Pantoprazole etc., are known potent proton pump inhibitors with powerful inhibitory action against the secretion of gastric juice (Lancet, Nov. 27, 1982 pages 1223-1224). They are used in the treatment of Zollinzer – Elision syndrome and stress related esophagitis ulceration. The derivatives are well known and are described, for example in EP-A 0005129.

It has been found that these benzimidazole derivatives, and in particular omeprazole, are susceptible to degradation in acid and neutral media. It is known to protect oral dosage forms of such benzimidazole derivatives by providing an enteric coating. In this way, the active material is protected from acidic gastric juices until it reaches the desired site of release, e.g. the small intestine. Because certain enteric coatings can themselves be, or contain, acidic material, it is also often required to protect the benzimidazole derivatives from the acidity of the enteric coating. For example, it is known to formulate the benzimidazole derivatives with an alkaline material before applying the enteric coating. It is also known to provide an intermediate coating between the benzimidazole derivative and the enteric coating. Generally the intermediate coating is selected so as to be substantially water-soluble or water-dispersible.

EP-A-024 7983; US 4,786,505; US 4,853,230 and US 5,385,739 describe oral pharmaceutical preparations containing benzimidazole derivatives that are potent inhibitors of gastric acid secretion, which are composed of a core material in the form of small beads or tablets containing one of the benzimidazole derivatives, particularly omeprazole, together with an alkaline reacting compound. The core material contains one or more inert reacting sub-coating layers thereon thereby providing a final outer enteric coating. Although the above-described compositions are reasonably stable over an extended period of storage, discoloration of the pellets and / or tablets with reduced gastric resistance and reduction of dissolution rate in alkaline buffers was observed.

More over the processes disclosed above are time consuming and laborious, involving many stages in manufacturing of the composition, consequently increasing the cost of the final composition.

In a German patent DE 32 22 476 a pharmaceutical composition has been described in which a soft gelatin capsule that is resistant to digestive juice, whose wall consists of a usual gelatin mass which contain polyvinyl acetate phthalate, hydroxypropyl methyl cellulose phthalate or a vinyl acetate / crotonic acid copolymer and/or an alkali metal salt, ammonia salt or amino salt of the same in their wall, which released their contents readily in the intestines within the prescribed time. The capsules are further treated on the surface with an aldehyde-coating agent.

The capsule shell composition described in DE 32 22 476 above, if used as such for manufacturing capsules containing one of the benzimidazole derivatives in a conventional manner, the free acidic groups of the polymer in the shell composition reacts with the benzimidazole derivatives and reduces the efficacy of the product during its storage / shelf life period.

The present invention takes as basis, the production of soft gelatin capsules in the conventional manner using gelatin mass in the known composition and to additionally incorporate substances into the gelatin shell which are insoluble up to a pH value of 5.5 in aqueous media, but quickly dissolve above pH value of 6.0

Considering the importance gained for the composition containing benzimidazole derivatives, particularly for the treatment of duodenal ulcers, there is a need for the development of pharmaceutical composition containing said derivatives having stability for an extended period during which period the composition does not get discoloured.

Accordingly, the main objective of the present invention is to provide an improved pharmaceutical composition containing Benzimidazole derivatives having enhanced stability during storage.

According to another objective of the present invention there is provided intestine dissoluble soft gel capsules composition consisting of gelatin and an enteric polymer in the form of a free acid or its salt characterised by the fact that the pharmaceutical composition consisting of benzimidazole derivatives, in particular omeprazole, incorporated in an oily base which is stable during shelf storage.

Still another objective of the invention is to provide a pharmaceutical composition for carrying the benzimidazole derivatives, to be filled into the soft gel capsules, that reduces degradation of the benzimidazole derivatives during storage / shelf life.

According to another feature of the invention there is provided a process for preparation of soft gel capsules containing benzimidazole derivatives that are resistant to the digestive / gastric juice comprising of a usual gelatin mass and an enteric polymer in the form of a free acid or as its salt.

Accordingly, the present invention provides an improved pharmaceutical composition in the form of a soft gel capsule resistant to gastric juice and soluble in intestine useful for the treatment of duodenal ulcers and related ailments which comprises of a gelatin shell resistant to gastric juice and soluble in intestine having an enteric polymer in the form of free acid or its salt, the capsule incorporating a composition comprising of a benzimidazole derivative, a hydrophobic oily substance or a mixture of such substances, an alkaline inert reacting material, a surface active agent and / or a solublising agent. The capsules are insoluble in aqueous medium up to a pH of 5.5 but quickly dissolve above pH of 6.0.

According to another feature of the present invention, there is provided a process for the preparation of a pharmaceutical composition in the form of a soft gel capsule resistant to gastric juice and soluble in intestine useful for the treatment of duodenal ulcers and related ailments which comprises forming a gelatin shell resistant to gastric juice and soluble in intestine having an enteric polymer in the form of free acid or its salt by conventional methods, incorporating into the resultant capsule a composition comprising of a Benzimidazole derivative, a hydrophobic oily substance or a mixture of such substances, an alkaline inert reacting material, a surface active agent and / or a solublising agent. The capsules are insoluble in aqueous medium up to a pH of 5.5 but quickly dissolve above pH of 6.0.

In a preferred embodiment of the invention, the enteric polymer used in the soft gel capsule composition may be selected from among the polymers but not limited to free acid forms of hydroxypropyl methyl cellulose phthalate, alkylmethacrylate and methacrylic acid ester copolymers, polyvinylacetate phthalate and the like or their ammonia or alkali metal salts. The amount of such enteric polymer employed may range from 5.0 – 40.0 percent, preferably 5.0 – 25.0 percent by weight with reference to the dried shell.

The gelatin mass into which the enteric polymer is incorporated is made up of a composition known in the art and contains gelatin, a plasticizer, preservatives, colourants, opacifiers, flavours etc., as required.

In order to carryout faster dissolution of the enteric polymer for preparing the capsule shell composition, the polymer is first dispersed in water, then aqueous solution of ammonia or alkali metal salt is mixed while stirring. When alkali metal salt is used it may be selected from substances such as sodium hydroxide, potassium hydroxide, carbonate of hydrogen sodium, carbonate of hydrogen potassium, sodium carbonate, potassium carbonate etc. The quantity of the base materials used is such that it is sufficient to neutralise 60 to 100 percent of the free acid groups present in the selected enteric polymer.

The excess ammonia or alkali has to be removed from the capsule shell composition to avoid decomposition of the ester couplings in enteric polymers. When aqueous ammonia solution is used to prepare polymer solution, the excess ammonia has to be removed before preparing the capsule
after mixing with the gelatin mass, by mixing the mass under reduced pressure in warm condition.

When alkali metal salts are used, the excess alkali is to be neutralized by treating the capsules with an acid selected from any of the following ones, hydrochloric acid, sulphric acid, nitric acid, phosphoric acid, mono carboxylic acids such as acetic acid, propionic acid, benzoic acid etc., dicarboxylic acids such as oxalic acid, maleic acid, fumaric acid etc. The acids are used in the form of cold aqueous solutions in the concentration range of 3 to 30% depending on the type of acid used. The acid treatment may be carried out after manufacturing and partial drying of the capsules to avoid deformation and / or leakage of the capsule contents.

According to another feature of the invention the soft gel capsules are optionally treated with a cross-linking agent that reacts with gelatin and makes it insoluble in gastric juice. The cross-linking agent may be selected from among the aldehydes such as formaldehyde, glutaraldehyde, crotonaldehyde 1,2-phthalic acid aldehyde, 1,3-phthalic acid aldehyde, 1,4-phthalic acid aldehyde or carbodiimides like 1-ethyl-3-[2-morpholinyl-(4)-ethyl]-carbodiimide-metho-p-toluene-sulfonate. The treatment may be done by either coating 0.05 to 1.0% w/v of the substance in an alcohol containing aqueous solution on to the soft gel capsule surface or mixing these substances in the gelatin mass before capsule manufacturing.

According to another feature of the invention the pharmaceutical composition containing benzimidazole derivative, known for its potent proton pump inhibition with powerful inhibitory action against the secretion of gastric juice, is prepared by suspending and/or solubilising the benzimidazole derivative in a carrier mixture composed of a hydrophobic oily carrier material, an alkaline inert reacting material and a surface active agent. The amount of such benzimidazole derivative used is equivalent to one unit dose recommended depending on the benzimidazole derivative incorporated i.e. for omeprazole the amount incorporated into enteric soft gel capsule may range from 10.0 to 60.0mg per capsule preferably 20.0 to 40.0 mg per capsule.

The hydrophobic oily material may be selected from among the following fats and oils: Fats and oils of vegetable origin such as sesame oil, corn, maize oil, soybean oil, sunflower oil, arachis oil, gingly oil etc.; animal oils such as fish oil, pig oil beef oil etc.; esters of straight chained aliphatic oils contained in glycerol such as Sunsoft 700 P-2 (a monoester substance manufactured by Taiho Chemicals Company) Panasete 810 (a triester substance, manufactured by Nippon Oils and Fats); hydrogenated vegetable oils or a mixture thereof. The amount of such hydrophobic oily material may range from 50.0 to 80.0 percent by weight with reference to the contents filled in capsule.

The alkaline buffering material present in the pharmaceutical composition may be selected from among but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminum salts of phosphoric acid, carbonic acid, citric acid, other suitable organic or inorganic acids; substances used in antacid preparations; meglumine; triethanolamine etc. The amount of such alkaline buffering material present in the composition may range from 5.0 to 40.0 percent, preferably 10.0 to 25.0 percent by weight with reference to the contents filled in capsule.

The surface active agent used as solubilising and / or dispersing agents is selected from among but are not restricted to substances such as glyceryl monostearate, polyoxyethylene castor oil derivatives such as Cremophor RH 40, Cremophor EL (Make : BASF Corporation), lecithin, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulphate, doccusate sodium etc. The amount of such surface active agent present in the composition may range from 2.0 to 20.0 percent preferably 5.0 to 15.0 percent by weight with reference to contents filled in capsule.

The seamless soft gel capsules can be manufactured on a rotary die machine filling with the liquid and / or semi solid composition containing benzimidazole derivatives.

The invention is described in detail in the examples given below which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention.

EXAMPLE – 1

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	35.0
Glycerin	17.5
Water	20.0
Hydroxypropyl methyl cellulose phthalate	7.5
Ammonia solution (25%w/v)	20.0

Gelatin mass is prepared by dispersing gelatin in a mixture of water and glycerin maintained at 70°C. Hydroxypropyl methylcellulose phthalate is dissolved by stirring in to ammonia solution at room temperature. The polymer solution is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) Composition of the medicament:

Name of the ingredient	**mg / Capsule**
Soybean oil	280.0
Omeprazole	20.0
Meglumine	20.0
Lecithin	30.0

Lecithin is dispersed into soybean oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) Manufacturing of capsule;

This gelatin mixture is transferred to the holding tank of rotary die capsulation machine for manufacture of capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by rotary die process.

EXAMPLE – 2

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	30.0
Glycerin	15.0
Water	20.0
Hydroxypropyl methyl cellulose phthalate	10.0
Ammonia solution (25%w/v)	25.0

Gelatin mass is prepared by dispersing gelatin in a mixture of water and glycerin maintained at 70°C. Hydroxypropyl methyl cellulose phthalate is dissolved by stirring in to ammonia solution at room temperature. The polymer solution is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) Composition of the medicament :

Name of the ingredient	mg / Capsule
Soybean oil	280.0mg
Omeprazole	20.0mg
Meglumine	20.0mg
Lecithin	30.0mg

Lecithin is dispersed into soybean oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of rotary die capsulation machine for manufacture of capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by rotary die process.

EXAMPLE – 3

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	40.0
Glycerin	17.5
Water	20.0
Hydroxypropyl methyl cellulose phthalate	5.0
Ammonia solution (25%w/v)	17.5

Gelatin mass is prepared by dispersing gelatin in a mixture of water and glycerin maintained at 70°C. Hydroxypropyl methyl cellulose phthalate is dissolved by stirring in to ammonia solution at room temperature. The polymer solution is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) Composition of the medicament:

Name of the ingredient	mg / Capsule
Soybean oil	280.0mg
Omeprazole	20.0mg
Meglumine	20.0mg
Lecithin	30.0mg

Lecithin is dispersed into soybean oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of rotary die capsulation machine for manufacture of capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by rotary die process.

EXAMPLE – 4

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	35.0
Glycerin	17.5
Water	25.0
Hydroxypropyl methyl cellulose phthalate	7.5
Ammonia solution (25%w/v)	15.0

Gelatin mass containing Hydroxypropyl methyl cellulose is prepared by dispersing Hydroxypropyl methyl cellulose phthalate in the form of a fine powder in a mixture of glycerin and water maintained at 70°C in which gelatin is dispersed to dissolve forming the gelatin mass. After cooling the mass to 45°C, ammonia solution is added slowly along the stirrer rod while stirring into the gelatin preparation tank. Stirring is continued till Hydroxypropyl methyl cellulose phthalate is completely dissolved. The mass is made bubble free by applying vacuum while maintaining the mass at 45 - 50°C under continuous mixing.

b) Composition of the medicament:

Name of the ingredient	mg / capsule
Soybean oil	200.0mg
Cremohor RH 40	40.0mg
Lansoprazole	30.0mg
Disodium hydrogen orthophosphate Anhydrous	30.0mg

Cremophor RH 40 is dispersed in soybean oil at 30°C. After cooling to room temperature Lansoprazole and disodium hydrogen orthophosphate are dispersed in to the mixture in the form of fine particles with the help of a mechanical stirrer and / or a homogeniser.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of rotary die capsulation machine for manufacture of capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by rotary die process.

EXAMPLE – 5

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	35.0
Glycerin	15.0
Water	20.0
Hydroxypropyl methyl cellulose phthalate	10.0
Sodium hydroxide solution 1% w/v	20.0

Gelatin mass is prepared by dispersing gelatin in a mixture of water and glycerin maintained at 70°C. Hydroxypropyl methyl cellulose phthalate is dissolved by stirring in to Sodium hydroxide solution at room temperature. Hydroxypropyl methyl cellulose phthalate solution in ammonia is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) Composition of the medicament:

Name of the ingredient	mg / capsule
Soybean oil	200.0mg
Hydrogenated vegetable oil	85.0mg
Lecithin	20.0mg
Pantoprazole sodium	45.0mg
Meglumine	20.0mg

Hydrogenated vegetable oil is melted and dispersed into soybean oil at 30 - 40°C followed by lecithin, meglumine and pantoprazole sodium and cooled to room temperature. The mixture is kneaded into a smooth paste using a triple roller mill.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of rotary die capsulation machine for manufacture of capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by rotary die process.

EXAMPLE – 6

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	30.0
Propylene glycol	15.0
Water	20.0
Hydroxypropyl methyl cellulose phthalate	10.0

Gelatin mass is prepared by dispersing in water at 70°C. Hydroxypropyl methyl cellulose phthalate is dissolved in propylene glycol at 60 - 70°C. and mixed with the gelatin mass to obtain uniform mixture.

b) Composition of the medicament:

Name of the ingredient	mg / Capsule
Soybean oil	280.0mg
Omeprazole	20.0mg
Meglumine	20.0mg
Lecithin	30.0mg

Lecithin is dispersed into soybean oil using a mechanical stirrer. Omeprazole and meglumine are added to the dispersion while stirring to obtain a smooth dispersion.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of rotary die capsulation machine for manufacture of capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by rotary die process.

EXAMPLE – 7

a) Composition of the Soft gelatin shell:

Name of the ingredient	Percent by wt.
Gelatin	35.0
Glycerin	17.5
Water	20.0
Polyvinylacetate phthalate (PVAP)	7.5
Ammonia solution (25%w/v)	20.0

Gelatin mass is prepared by dispersing gelatin in a mixture of water and glycerin maintained at 70°C. Polyvinylacetate phthalate is dissolved by stirring in to ammonia solution at room temperature. Polyvinylacetate phthalate solution in ammonia is added to gelatin mass while stirring the mass maintained at 45 - 50°C. Vacuum is applied to the mixing vessel to remove the ammonia evolved and to obtain bubble free transparent mixture of polymer solution and gelatin mass.

b) Composition of the medicament:

Name of the ingredient	mg / capsule
Sunflower oil	200.0mg
Cremohor RH 40	40.0mg
Lansoprazole	30.0mg
Disodium hydrogen orthophosphate Anhydrous	30.0mg

Cremophor RH 40 is dispersed in sunflower oil at 30°C. After cooling to room temperature Lansoprazole and disodium hydrogen orthophosphate are dispersed into the mixture in the form of fine particles with the help of a mechanical stirrer and / or a homogeniser.

c) Manufacturing of capsule:

This gelatin mixture is transferred to the holding tank of rotary die capsulation machine for manufacture of capsule shell. The dispersion containing medicament is transferred to the hopper of the capsulation machine for filling into the soft gel capsules. The soft gel capsules are manufactured by rotary die process.

Advantages of the invention:

The advantages of the present invention are:

1) Simple method of manufacturing, when compared to the methods disclosed in the prior art.

2) Improved bioavailability when compared to the solid enteric coated pellets as the medicament is solublised or suspended in the form of very fine particles in the liquid / semisolid pharmaceutical composition filled into the soft gel capsule.

We claim:

1. An improved pharmaceutical composition in form of a soft gel capsule resistant to gastric juice and soluble in intestine useful for the treatment of duodenal ulcers and related ailments which comprises of a gelatin shell resistant to gastric juice and soluble in intestine having an enteric polymer in the form of free acid or its salt, the capsule incorporating a composition comprising of a benzimidazole derivative, a hydrophobic oily substance or a mixture of such substances, an alkaline inert reacting material, a surface active agent and / or a solublising agent; where the capsules are insoluble in aqueous medium up to a pH of 5.5 but quickly dissolve above pH of 6.0.

2. An improved pharmaceutical composition as claimed in claim 1 where in the benzimidazole derivative, is selected from medicaments such as omeprazole, lansoprazole, pantoprazole, timoprazole and the like.

3. An improved pharmaceutical composition as claimed in claims 1 & 2 where in the amount of benzimidazole derivative in the formulation is equivalent to one unit dose of selected benzimidazole derivative.

4. An improved pharmaceutical composition as claimed in claims 1 to 3 where in the enteric polymer employed in the gelatin shell is selected from polymers such as hydroxypropyl methyl cellulose phthalate, alkyl methacrylate and methacrylic acid copolymers, polyvinyl acetate phthalate and the like in the form of free acid or their ammonia or alkali metal salts.

5. An improved pharmaceutical composition as claimed in claims 1 & 4 where in the amount of enteric polymer employed in the gelatin shell ranges from 5.0 to 40.0 percent, preferably 5.0 to 25.0 percent by weight, with reference to the dried shell.

6. An improved pharmaceutical composition as claimed in claims 1 to 5 where in the benzimidazole derivative in the formulation is suspended / solubilised in a hydrophobic oily substance selected from fats and oils of vegetable origin such as sesame oil, corn oil, maize oil, soybean oil, sunflower oil, arachis oil, gingly oil and the like; animal origin such as fish oil, pig oil, beef oil and the like; esters of straight chain aliphatic oils such as Sunsoft 700 P-2 (Taiho chemical company) Panasete 810 (Nippon oils and Fats); hydrogenated vegetable oils or a mixture thereof.

7. An improved pharmaceutical composition as claimed in claims 1 to 6 where in the amount of hydrophobic oily substance used in the formulation ranges from 50.0 to 80.0 percent by weight, with reference to the contents filled in capsules.

8. An improved pharmaceutical composition as claimed in claims 1 to 7 where in materials such as glyceryl monostearate, lecithin, polyoxyethylene castor oil derivative such as Cremophor RH 40, Cremophor EL (BASF) polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulphate, docusate sodium and the like is used as surface active agents.

9. An improved pharmaceutical composition as claimed in claims 1 to 8 where in the amount of surface active agent and/or solublising agent incorporated into the formulation ranges from 2.0 to 20.0 percent, preferably 5.0 to 15.0 percent by weight, with reference to the contents filled in capsule.

10. An improved pharmaceutical composition as claimed in claims 1 to 9 where in materials such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid, other suitable organic or inorganic acids; substances used in antacid preparations; meglumine; triethanolamine and the like is used as alkaline inert reacting materials.

11. An improved pharmaceutical composition as claimed in claims 1 to 10 where in the amount of alkaline inert reacting substance incorporated in the formulation ranges from 5.0 to 40.0 percent, preferably 10.0 to 25.0 percent by weight, with reference to the contents filled in capsule.

12. An improved pharmaceutical composition as claimed in claims 1 to 11 where in the soft gel capsules are treated with a gelatin cross linking agent such as formaldehyde, glutaraldehyde, crotonaldehyde, 1,2-phthalic acid aldehyde, 1,3-phthalic acid aldehyde, 1,4-phthalic acid aldehyde; carboimides such as 1-ethyl-3-[2-morpholinyl-(4)-ethyl]-carboimide-metho-P-toluene-sulfonate and the like.

13. An improved pharmaceutical composition as claimed in claims 1 to 12 where in the soft gel capsules are treated with cold dilute solutions of acids selected from hydrochloric acid, sulphuric acid, nitric acid, phosphoric acid, citric acid, propionic acid, benzoic acid, oxalic acid, maleic acid, fumaric acid and the like.

14. A process for the preparation of a pharmaceutical composition in the form of a soft gel capsule resistant to gastric juice and soluble in intestine useful for the treatment of duodenal ulcers and related ailments which comprises forming a gelatin shell resistant to gastric juice and soluble in intestine having an enteric polymer in the form of free acid or its salt, incorporating into the resultant capsule a composition comprising of a benzimidazole derivative, a hydrophobic oily substance or a mixture of such substances, an alkaline inert reacting material, a surface active agent and / or a solublising agent; where the resultant capsules are insoluble in aqueous medium up to a pH of 5.5 but quickly dissolve above pH of 6.0.

15. A process as claimed in claim 14 where in the benzimidazole derivative is selected from medicaments such as omeprazole, lansoprazole, pantoprazole, timoprazole and the like.

16. A process as claimed in claims 14 & 15 where in the amount of benzimidazole derivative used in the formulation is equivalent to one unit dose of selected benzimidazole derivative.

17. A process as claimed in claims 14 to 16 where in the enteric polymer employed in the gelatin shell is selected from polymers such as hydroxypropyl methyl cellulose phthalate, alkyl methacrylate - methacrylic acid copolymers, polyvinyl acetate phthalate and the like in the form of free acid or their ammonia or alkali metal salts.

18. A process as claimed in claims 14 & 17 where in the amount of enteric polymer employed in the gelatin shell ranges from 5.0 to 40.0 percent preferably 5.0 to 25.0 percent by weight with reference to the dried shell.

19. A process as claimed in claims 14 to 18 where in the enteric polymer is incorporated into gelatin mass, in the form of a free acid or its ammonia or alkali metal salt by dispersing the free acid or its salt into the gelatin mass at 45 - 50°C using a top driven mechanical stirrer.

20. A process as claimed in claims 14 to 19 where in the hydrophobic oily substance employed in the formulation is selected from fats and oils of vegetable origin such as sesame oil, corn oil, maize oil, soybean oil, sunflower oil, arachis oil, gingly oil and the like; animal origin such as fish oil, pig oil, beef oil and the like; esters of straight chain aliphatic oils such as Sunsoft 700 P-2 (Taiho chemical company) Panasete 810 (Nippon oils and Fats); hydrogenated vegetable oils or a mixture thereof.

21. A process as claimed in claims 14 to 20 where in the amount of hydrophobic oily substance used in the formulation ranges from 50.0 to 80.0 percent by weight with reference to the contents filled in capsules.

22. A process as claimed in claims 14 to 21 where in the materials such as glyceryl monostearate, lecithin, polyoxyethylene castor oil derivative such as Cremophor RH 40, Cremophor EL (BASF) polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulphate, docusate sodium and the like is used as surface active agent.

23. A process as claimed in claims 14 to 22 where in the amount of surface active agent and/or solublising agent incorporated into the formulation ranges from 2.0 to 20.0 percent, preferably 5.0 to 15.0 percent by weight, with reference to the contents filled in capsule.

24. A process as claimed in claims 14 to 23 where in materials such as the sodium, potassium, calcium, magnesium and aluminum salts of phosphoric acid, carbonic acid, citric acid, other suitable organic or inorganic acids; substances used in antacid preparations; meglumine; triethanolamine and the like is used as alkaline reacting material.

25. A process as claimed in claims 14 to 24 where in the amount of alkaline inert reacting material used in the formulation ranges from 5.0 to 40.0 percent, preferably 10 to 25.0 percent by weight, with reference to the contents fill in capsule.

26. A process as claimed in claims 14 to 25 where in the soft gel capsules are treated with a gelatin cross linking agent such as formaldehyde, glutaraldehyde, crotonaldehyde, 1,2-phthalic acid aldehyde, 1,3-phthalic acid aldehyde, 1,4-phthalic acid aldehyde; carboimides such as 1-ethyl-3-[2-morpholinyl-(4)-ethyl]-carboimide-metho-P-toluene-sulfonate and the like.

27. A process as claimed in claims 14 to 26 where the gelatin capsules are treated with a gelatin cross linking agent either as coating on to the surface of capsules in the form of a solution in an alcohol containing aqueous solution or mixing in the gelatin mass before capsule manufacture in a concentration ranging from 0.05 to 1.0 percent by weight of the gelatin mass.

28. A process as claimed in claims 14 to 27 where in the soft gel capsules are treated with cold dilute solutions of acids selected from hydrochloric acid, sulphuric acid, nitric acid, phosphoric acid, citric acid, propionic acid, benzoic acid, oxalic acid, maleic acid, fumaric acid and the like.

29. An improved pharmaceutical composition in the form of a soft gel capsule resistant to gastric juice and soluble in intestine useful for the treatment of duodenal ulcer and related ailments substantially as herein described with reference to the Examples 1 to 7.

30. A process for the preparation of pharmaceutical composition in the form of a soft gel capsule resistant to gastric juice and soluble in initiated useful for the treatment of duodenal ulcer and related ailments substantially as herein described with reference to the examples 1 to 7.

Dated this 4th day of April, 2000

(P.R.HADGAPATHI)
Director - Tech. Services
Natco Pharma Limited

ABSTRACT

The present invention relates to a pharmaceutical composition in the form of a soft gel capsule resistant to gastric juice and dissoluble in intestine and is suitable for incorporating a benzimidazole derivative which require protection from acidic gastric juice until it reaches the small intestine, comprises of a gelatin and an enteric polymer in the form of the free acid or its salt. The surface of the soft gel capsule may optionally be treated with a gelatin cross linking agent and / or an acid solution to partially convert the polymer salt to free acid and a method for preparing such soft gel.

The pharmaceutical composition carrying a benzimidazole derivative either in suspension or solution comprises of hydrophobic oily substance, an alkaline inert reacting substance and a surface active agent.

To,
The Controller of Patents,
The Patent Office Branch,
Chennai.

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FORM 5

THE PATENT ACT 70
(39 of 1970)

DECLARATION AS TO INVENTORSHIP

(See Rule 14(5))

We, NATCO PHARMA LIMITED an Indian Company registered under the Indian Companies Act. 1956, having its registered office at NATCO House, Road No.2, Banjara Hills, Hyderabad – 33, India,

hereby declare that the true and first inventors of the invention disclosed in the complete specification filed in pursuance of our application No.: 968 / MAS /99, dated 01 / 10 / 1999.

a) VENKATESWARA RAO PAVULURI,

and

b) KHADGAPATHI PODILI

all of NATCO PHARMA LTD, NATCO House, Road No.2, Banjara Hills, Hyderabad – 33, India; all Indian citizens.

Dated this 24th day April of 2000

(DR.P.KHADGAPATHI)
Director – Technical services
For NATCO PHARMA LTD.

To,
The Controller of Patents,
The Patent Office Branch,
Chennai.